University of Zurich[UZH]

Clinical Research Priority Program Multiple Sclerosis - CRPP[MS]

Scientific Program, Biographical Sketches and Poster Abstracts

CRPP MS

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Clinical Research Priority Program Multiple Sclerosis

Symposium

«Heterogeneity of Autoimmune Diseases»

12.06.– 13.06.2017

Confirmed Speakers

Sergio Baranzini, University of California
Burkhard Becher, University of Zurich
Onur Boyman, University Hospital Zurich
Tobias Derfuss, University of Basel
Simon Fillatreau, INEM, Paris
Anke Henning, University of Greifswald
Reinhard Hohlfeld, University of Munich
Matilde Inglese, Mount Sinai Hospital, New York
Lars Klareskog, Karolinska Institute
Ingrid Kockum, Karolinska Institute
Hans Lassmann, University of Vienna
Edgar Meinl, University of Munich
Marco Prinz, University of Freiburg
Gerhard Rogler, University Hospital Zurich
Lawrence Steinman, Stanford University
Maarten Titulaer, Erasmus University Rotterdam

Location:
University Hospital Zurich,
Grosser Hörsaal OST

Gloriastrasse 29, 8091 Zurich

Registration (required) via
www.multiplesclerosis.uzh.ch

Abstract submission deadline:
16.04.2017

Registration free of charge until
29.05.2017

After 29.05.17, an administrative fee of CHF 80.– will be charged.

CRPP[MS] Speakers

Andreas Lutterotti, USZ; Roland Martin, USZ;
Christian Münz, UZH; Sven Schippling, USZ;
Mireia Sospedra, USZ;
Young Researchers of the CRPP[MS]

University of Zurich[UZH]

UniversityHospital Zurich

CRPP MS

Dear colleagues,

It is our pleasure to welcome you to our first international CRPP[MS] Symposium under the title „Heterogeneity of Autoimmune Diseases" on the 12th to 13th of June 2017 in Zurich.

Autoimmune diseases are of complex nature based on an abnormal immune response against our body's own tissues and organs. Multiple Sclerosis (MS) is such a prototypic autoimmune disease, which affects the central nervous system (CNS) and leads to neurological signs and symptoms, e.g. problems with vision, sensation, motor-, coordination-, and neurocognitive deficits. Currently, there is no cure for MS and also no reliable way to predict future course and -severity. MS is caused by a complex genetic trait and by several environmental risk factors. These etiologic factors act in concert and translate into the main pathomechanisms, autoimmune inflammation, demyelination and axonal/neuronal damage. Depending on their extent the above symptoms, imaging findings and response to treatment vary greatly. Disease heterogeneity is not only a hallmark of MS, but also of other autoimmune diseases and generally of many human illnesses. In the Clinical Research Priority Program Multiple Sclerosis (CRPP[MS]), we aim to define phenotypic subgroups of MS by imaging, electrophysiological- and modeling approaches, to characterize the underlying biology in several subprojects, and finally to develop novel treatments. Understanding disease heterogeneity offers to provide new insights about pathomechanisms of MS, improve the diagnosis and treatment of patients, and eventually pave the way towards personalized medicine.

The conference «Heterogeneity of Autoimmune Diseases» is an important event for the CRPP[MS], which is part of the University of Zürich's efforts to promote clinical research and foster research excellence. One important goal is to establish a network of scientists and clinicians with different expertise to address the above research topics and disease heterogeneity of MS from several different angles and with innovative approaches. Further, the CRPP[MS] plays a key role in setting up a translational research infrastructure that bridges between the main academic institutions in Zurich, the University Zurich (UZH), the Swiss Federal Institute of Technology (ETHZ) and the University Hospital Zurich (USZ).

The conference shall serve as a platform to share new data, inform a broader audience about the latest research in the field and present our network at an international level. We hope to learn not only from leading experts in the field of MS, but also from colleagues, who pursue similar issues in other autoimmune diseases.

We are happy to welcome speakers and guests and look forward to an exciting symposium!

Roland Martin, Sven Schippling, Andreas Lutterotti and Karolin Léger

Zürich, June 2017

This symposium is supported by

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Program

12th of June 2017

08:30 – 09:00	Registration
09:00 – 09:10	Welcome by Michael Hengartner, president of the University of Zurich
09:10 – 09:20	Welcome by the directors of the CRPP[MS]
Session 1	**Chair: Roland Martin**
09:20 – 10:05	**Keynote lecture 1 Lawrence Steinman**, Stanford University "Molecular guardians in the brain - natural protectors from neuroinflammation and neurodegeneration in MS"
10:05 – 10:30	**Sergio E. Baranzini,** University of California "Genes vs environment: The influence of human and bacterial genomes in MS susceptibility"
10:30 – 11:00	*Break*
11:00 – 11:25	**Marco Prinz**, University of Freiburg "Origin and fate of myeloid cells in the CNS"
11:25 – 11:50	**Burkhard Becher**, University of Zurich "Communication between T cells and myeloid cells in chronic inflammation"
11:50 – 12:35	**Keynote lecture 2 Gerhard Rogler,** University Hospital Zurich "Pathogenesis of inflammatory bowel disease: Genes, bugs and environment"
12:35 – 14:00	*Lunch and Poster Session*
Session 2	**Chair: Andreas Lutterotti**
14:00 – 14:25	**Christian Münz**, University of Zurich "Synergies between genetic risk factors and viral infections in MS"
14:25 – 14:50	**Tobias Derfuss**, University of Basel "B cells and Multiple Sclerosis"
14:50 – 15:15	**Matilde Inglese**, Mount Sinai Hospital, NY ""UNICUIQUE SUUM": The contribution of cerebellar lobules atrophy to disability in progressive MS"
15:15 – 15:45	*Break*
15:45 – 16:25	**Young Researchers CRPP[MS]** Poster Blitz
16:25 – 16:50	**Anke Henning**, Ernst-Moritz Arndt University, Greifswald and Max Planck Institute for Biological Cybernetics, Tübingen, Germany "Metabolic alterations in MS detected by magnetic resonance spectroscopy at 3T and 9.4T"
16:50 – 17:15	**Sven Schippling**, University of Zurich "Phenotyping Multiple Sclerosis and EAE using multimodal imaging"
17:15	Closing Remarks Day 1 and Apéro

13th of June 2017

09:00 – 09:05	Welcome Day 2
Session 3	**Chair: Sven Schippling**
09:05 – 09:50	**Keynote lecture 3 Lars Klareskog**, Karolinska Insitutet "Pathogenesis of rheumatoid arthritis; From triggering to targeting"
09:50 – 10:15	**Onur Boyman**, University Hospital Zurich "IL-2-based approaches for induction of immune tolerance"
10:15 – 10:40	**Roland Martin**, University of Zurich "Role of the DR15 haplotype in MS"
10:40 – 11:10	*Break*
11:10 – 11:35	**Simon Fillatreau**, INEM Paris "Cytokine-producing B cells and plasma cells: novel regulators of autoimmune diseases"
11:35 – 12:00	**Mireia Sospedra**, University Hospital Zurich "Search for candidate autoantigens in Multiple Sclerosis"
12:00 – 12:25	**Maarten Titulaer**, Erasmus University Rotterdam "Autoimmune Encephalitis: antibodies you do not want to miss"
12:25 – 14:00	*Lunch and Poster Session*
Session 4	**Chair: Mireia Sospedra**
14:00 – 14:45	**Keynote lecture 4 Hans Lassmann**, University of Vienna "Relapsing versus Progressive Multiple Sclerosis: Pathology and Disease Mechanisms"
14:45 – 15:10	**Reinhard Hohlfeld**, University of Munich "What can twin studies tell us about the beginnings of MS?"
15:10 – 15:35	**Ingrid Kockum**, Karolinska Insitutet "Heterogeneity in MS – approached by studying gene and life-style exposure interactions."
15:35 – 16:00	*Break*
16:00 – 16:25	**Edgar Meinl**, University of Munich "Humoral immunity in multiple sclerosis"
16:25 – 16:45	**Ivan Jelcic**, University of Zurich – Young Researchers Talk "Proinflammatory B Cells drive brain-homing and pathogenic T helper cells in Multiple Sclerosis"
16:45 – 17:10	**Andreas Lutterotti**, University of Zurich "Antigen-coupled cells to induce immuntolerance in MS"
17:10	Poster Award and Closing Remarks Day 2

PLENARY TALKS

Biographical Sketches

Lawrence Steinman
Neurology & Neurological Sciences
Stanford University, Stanford, USA

Keynote lecture 1
"Molecular guardians in the brain-natural protectors from neuroinflammation and neurodegeneration in MS"

Biographical Sketch of Lawrence Steinman

Steinman is Professor of Neurology, Neurological Sciences and Pediatrics at Stanford University and Chair of the Stanford Program in Immunology from 2001 to 2011. His research focuses on what provokes relapses and remissions in multiple sclerosis (MS) and in neuromyelitis optica (NMO) and the quest for antigen specific therapy. He is developing a small molecule therapeutic in trials for Huntington's Disease. Steinman identified guardian molecules in brain that have protective properties in a number of inflammatory conditions. These protective molecules activate regulatory B cells.

Steinman was senior author on the 1992 Nature article that led to the drug Tysabri, approved for MS and Crohn's disease.

Dr. Steinman graduated from Dartmouth College, Magna Cum Laude in Physics. His MD is from Harvard Medical School. He was a post-doctoral fellow in chemical immunology fellow at the Weizmann Institute of Science. After neurology residency he remained on the faculty in 1980. He has received numerous honors, including the John M. Dystel Prize in 2004, the Javits Neuroscience Investigator Award from the NINDS twice, the Charcot Prize in MS research, and the Cerami Prize in Translational Medicine. Steinman is a member of the National Academy of Sciences, and the National Academy of Medicine.

Dr. Steinman holds 44 patents. He cofounded several biotech companies. He was a Director of Centocor from 1988 until its sale to Johnson and Johnson.

Sergio E. Baranzini
Department of Neurology
University of California, San Francisco, USA

"Genes vs environment: The influence of human and bacterial genomes in MS susceptibility"

Biographical Sketch of Sergio E. Baranzini

Sergio E. Baranzini is Professor In-Residence in the Department of Neurology at the University of California San Francisco (UCSF). He is also a member of the Graduate Program in Bioinformatics, the Institute for Human Genetics, and of the California Institute for Quantitative Biology (QB3). He holds the Heidrich Friends and Family endowed chair in Neurology.
Dr. Baranzini earned his degrees in clinical biochemistry (1992) and PhD in human molecular genetics (1997) from the University of Buenos Aires, Argentina. Dr. Baranzini then moved to UCSF to specialize in the analysis of complex hereditary diseases, and focused his efforts on multiple sclerosis. His current research involves the large throughput analysis of samples from MS patients to characterize the activity of genes during different stages of the disease, differential response to treatment, and disease progression. In addition Dr. Baranzini collaborates with several interdisciplinary teams worldwide to integrate all the available knowledge obtained in different research domains in an approach known as systems biology. Dr Baranzini's current research also involves immunological studies using the EAE model, sequencing of whole genomes and transcriptomes from patients with multiple sclerosis and developing bioinformatics tools to integrate this information with that coming from other high throughput technologies. He also leads the iMSMS, an international consortium study the effect of bacterial populations (microbiota) on MS susceptibility and progression.

Dr. Baranzini has published his research on MS in several top-tier journals like Science, Nature, PNAS, J Immunol, and PLoS Biol. He is a member of the International Multiple Sclerosis Genetics Consortium, the American Association of Immunologists, and an elected member of the American Neurological Association and the International Society of Neuroimmunology. He is also a member of the Editorial Board of the *MS Journal*, *Neurology* and *mSystems* in addition to serving as an ad-hoc reviewer for several other scientific publications in including Nature Medicine, PNAS, and the Am J Hum Genet.

Marco Prinz
Institute of Neuropathology
University of Freiburg, Freiburg, Germany

"Origin and fate of myeloid cells in the CNS"

Biographical Sketch of Marco Prinz

Dr. Prinz obtained his MD at the Charitè, Humboldt-University Berlin in 1997. During his MD thesis he investigated the pathology of cortical interneurons in humans at the Institute of Neuroanatomy at the Charitè Berlin. He did a postdoc at the Max-Delbrück-Centre (MDC) of Molecular Medicine dedicated to the function of glial cells in the central nervous system (CNS), especially microglia. He performed his residency in Neuropathology at the University Hospital Zurich, Switzerland and studied there the role of the peripheral and CNS-restricted immune system for the pathogenesis of neurodegenerative diseases such as prion diseases. In 2003 he became a group leader at the University Hospital in Göttingen, Germany and in 2007 lecturer of Neuropathology there.

He was recruited to the University of Freiburg, Germany, in 2008 and was promoted to the rank of Full Professor and Chair of the Institute of Neuropathology.

Dr. Prinz laboratory studies the mechanisms that regulate the development and function of the mononuclear phagocyte lineage in the central nervous system including microglia, perivascular and meningeal macrophages. His laboratory has made seminal discoveries in CNS macrophage biology revealing their embryonic origin and their local maintenance in situ. Dr. Prinz belongs to several German Research Foundation (DFG)- and EU-funded scientific consortia to decipher the transcriptional regulation of the macrophage lineage in the CNS.
Currently, his research group aims to understand myeloid cell biology in the CNS during health and disease and studies the impact of the immune system on the pathogenesis of neurological disorders such as neurodegenerative diseases, ultimately aimed at recognizing novel therapeutic strategies and targets to treat these central nervous system diseases.

Dr. Prinz has authored more than 170 primary papers and reviews in high profile journals and has obtained extensive DFG and EU funding for his studies on macrophage biology in the CNS in mice and humans.

Burkhard Becher
Institute of Experimental Immunology
University of Zurich, Zurich, Switzerland

"Communication between T cells and myeloid cells in chronic inflammation"

Biographical Sketch of Burkhard Becher

Burkhard Becher, PhD is since 2008 Professor and Co-Chairman of the Institute of Experimental Immunology at the University of Zurich, Switzerland. He studied Biology at the University of Cologne, Germany. He started his graduate studies at McGill University, Canada in 1994 where he studied microglia biology, followed 1999 by post-doctoral research at Dartmouth Medical School, USA, where he learned the use of i*n vivo* models of disease. His labs research focuses is on the role of cytokines in inflammation using primarily animal models of autoimmunity and cancer as well as high-dimensional analysis of human patients.

Abstract
Many chronic inflammatory diseases are thought to be driven by autoimmune T cells. This is mostly due to the fact that many of these diseases have the MHC locus as a risk allele and that animals can be immunized with a T cell epitope for an auto-antigen to develop disease. However, deregulated cytokines are also a hallmark of chronic inflammation and in some diseases (e.g. psoriasis) it is becoming increasingly clear that cytokine deregulation is the cause of tissue inflammation. I propose that deregulated cytokine expression is the culprit behind many of the chronic inflammatory diseases and that T cells are only the instigators rather than executers of immunopathology. T cells can activate myeloid cells, which represent the primary infiltrate in chronic inflammatory diseases. I will discuss how T cells instruct myeloid cells to do their bidding.

Gerhard Rogler
Department of Gastroenterology
University Hospital Zurich, Zurich, Switzerland

Keynote lecture 2
"Pathogenesis of inflammatory bowel disease: Genes, bugs and environment"

Biographical Sketch of Gerhard Rogler

Gerhard Rogler (*22.07.1963) received his approbation as physician and M.D. degree from the University of Ulm, Germany in 1992 and his Ph.D. degree after studying philosophy in Ulm and Augsburg, Germany in 1996. After an internship (Dept. of Internal Medicine II, University of Ulm) from 1991 to 1992 he was a postdoctoral fellow at the Institute of Clinical Chemistry and Pathobiochemistry, University of Regensburg (Director Prof. Dr. Gerd Schmitz) between 1992 and 1994. In 1994 he changed to the Department of Internal Medicine I, University of Regensburg (Director Prof. Dr. Jürgen Schölmerich) to work as a clinical and research fellow. After receiving his Internal Medicine Boards in 1999, Gerhard Rogler became attending physician and senior lecturer. In 1999 he received a prestigious Heisenberg Award of the Deutsche Forschungsgemeinschaft. From 2000 to 2001 Gerhard Rogler was Visiting Scholar at the Center of Molecular Medicine, University of San Diego, San Diego California. In 2003 Gerhard Rogler became associate professor and head of the Div. of Gastroenterology and Hepatology at the University of Regensburg, Germany. Since 2007 he is full professor of Gastroenterology and Hepatology at the University of Zürich. He has built up a center for IBD treatment and research. His fields of research are mucosal inflammation, innate immunity, IBD, intestinal fibrosis, inflammation associated colon cancer, GvHD. Gerhard Rogler has been elected to become chief of the Department of Gastroenterology and Hepatology in Zürich by August 1st 2017. Gerhard Rogler has published more than 450 Pubmed-listed manuscripts with a cumulative impact factor of > 3000, has more than 15.000 citations and a h-index of 63. He received numerous awards such as the "Honorary Award 2013" of the Swiss Gastroenterology Society, SGG, the LeVaillant award in 2015 and the honorary membership of the South African Society of Gastroenterology (SAGES) in 2013. Gerhard Rogler is member of the Governing Board of the European Crohn's and Colitis Organization (ECCO) and member of the International Organization of IBD Research (IOIBD).

Christian Münz
Institute of Experimental Immunology
University of Zurich, Zurich, Switzerland

"Synergies between genetic risk factors and viral infections in MS"

Biographical Sketch of Christian Münz

Christian Münz has been trained in immunology at the German Cancer Research Institute, the University of Tübingen, Germany, and the Rockefeller University in New York, USA. He became Assistant Professor and Head of Laboratory at the Rockefeller University in 2003. In 2008 he was recruited as Associate Professor and Co-Director of the Institute of Experimental Immunology to the University of Zürich, Switzerland, and became Full Professor in 2015. Since 2010 he is also Visiting Professor at the Imperial College in London, UK. In 2006 he received the Burroughs Welcome Fund Investigators in Pathogenesis of Infectious Disease Award for his studies on antigen processing via macroautophagy, and in 2012 the Sobek Award for his studies on the association of Epstein Barr virus (EBV) infection with multiple sclerosis (MS). He is an expert in EBV specific immune control and autophagy, and has published more than 200 papers and book chapters on these topics. His recent work expands to the modulation of EBV specific immune control by genetic variations that predispose for MS.

Tobias Derfuss
Department of Neurology
University of Basel, Basel, Switzerland

"B cells and Multiple Sclerosis"

Biographical Sketch of Tobias Derfuss

Tobias Derfuss is a clinical neurologist with a specialisation in neuroimmunology. He received his clinical training at the Department of Neurology, Klinikum Grosshadern in Munich. His research at the Max-Planck Institute for Neurobiology, Department of Neuroimmunology, was focussed on the discovery of new autoantigens in Multiple Sclerosis and the characterisation of the immune response against latent herpesviruses. After training in neuromuscular diseases at the Friedrich-Baur Institute and in psychiatry at the Max-Planck Institute for Psychiatry in Munich he was appointed head of the out-patient department and MS clinic at the Department of Neurology of the university clinic in Erlangen.
Since 2010 he is professor and senior physician at the Department of Neurology and the Department of Biomedicine at the university clinic in Basel. His main research focus is the discovery of biomarkers and analyzing the mode of action of disease modifying treatments in MS. Especially the role of B cells in the pathogenesis of MS and the interaction of B cells with their target cells is explored in cell culture as well as in *in vivo* models. Dr. Derfuss is also involved in the design and conduct of clinical trials for newly emerging therapies in MS.

Matilde Inglese
Icahn School of Medicine
Mount Sinai Hospital, New York, USA

""UNICUIQUE SUUM": The contribution of cerebellar lobules atrophy to disability in progressive MS"

Biographical Sketch of Matilde Inglese

Matilde Inglese is an Associate Professor of Neurology, Radiology and Neuroscience, at the Icahn School of Medicine at Mount Sinai in New York. She trained as a neurologist in Genoa, Italy, where she completed her fellowship in multiple sclerosis. Dr. Inglese then moved to San Rafael Hospital in Milan where she was trained in neuroimaging. In 2002, after obtaining a PhD in Neuroscience as part of a joint program between the University of Genoa and the New York University, she moved to New York where she joined NYU as a faculty member. In 2011, after her tenure as an Associate Professor of Radiology, Neurology and Biomedical Imaging at New York University, she moved to Mount Sinai, where she directs the Research Imaging Program in the department of Neurology. Her Research has a clinical and translational focus by investigating novel clinical outcomes of MS-related neurological deficits and in vivo mechanisms of brain injury and repair by means of neuroimaging techniques. Dr. Inglese's research is funded by grants from the National Institute for Neurological Disorders and Stroke, by the National Multiple Sclerosis Society and by the Congressionally Directed Medical Research Program in Multiple Sclerosis. She has authored and co-authored more than 150 publications in peer-reviewed journals, including Lancet, Lancet Neurology, Annals of Neurology, Brain and Neurology. She is on the editorial board of peer-reviewed journals and she has served on grant advisory panels for the National Institute of Health, the National Multiple Sclerosis Society and for several international funding agencies.

Anke Henning
Institute of Physics
Ernst-Moritz Arndt University, Greifswald and
Max Planck Institute for Biological Cybernetics, Tübingen,
Germany

"Metabolic alterations in MS detected by magnetic resonance spectroscopy at 3T and 9.4T"

Biographical Sketch of Anke Henning

Anke Henning is full professor in the Institute of Physics at the University of Greifswald, Germany since May 2017. She studied physics at the Technical University Chemnitz. Afterwards she did her PhD at the Institute of Biomedical Engineering at ETH Zurich in the field of high field magnetic resonance spectroscopy under the supervision of Prof. Bösiger. From 2008 to mid 2012 she was project leader at the same Institute and built up a reasearch group focusing on magnetic resonance spectroscopy methods development and applications. In June 2012 she became research group leader at the Max Planck Institute of Biological Cybernetics in Tübingen, Germany with access to a 9.4T human whole-body MRI scanner. Her research interests are in ultra-high field magnetic resonance imaging with a focus on the development of novel metabolic imaging methods and corresponding enabling technology.

Sven Schippling
Department of Neurology
University of Zurich, Zurich, Switzerland

"Phenotyping Multiple Sclerosis and EAE using multimodal imaging"

Biographical Sketch of Sven Schippling

Sven Schippling was appointed to the 'Multimodal Imaging in Neurology' Professorship at the University of Zurich in August 2015. He is a senior neurologist and head of the Neuroimmunology outpatient unit at the Department of Neurology, University Hospital and University of Zurich, Switzerland. He is a Co-Director of the Clinical Research Priority Program on Multiple Sclerosis (CRPP^{MS}) of the University of Zurich and a Senior Group Leader at the Neuroscience Center Zurich, Federal Institute of Technology (ETH), Zurich.
Sven Schippling received his medical degree from the University of Hamburg, Germany. He has completed post-doctoral research fellowships at the Institute for Molecular Cell Biology Hamburg-Eppendorf, and at the Institute of Neurology, University College London, UK from 2005-2006. He received his board certification in neurology in 2008.
Sven Schippling's research interests centre on structural and quantitative magnetic resonance imaging (MRI) and optical coherence tomography in MS and neuromyelitis optica spectrum disorders (NMOSD), the development of novel imaging-based outcome measures for Phase II proof-of-concept clinical trials in MS, and systems electrophysiology/transcranial magnetic stimulation. His research is supported by the Clinical Research Priority Program of the University of Zurich, the Betty and David Koetser Foundation for Brain Research and The Swiss MS Society.
He is a founding member of the Neuromyelitis Optica Study Group (NEMOS), Germany, and the IMSVISUAL network, an international group of experts in the field of vision related outcoms in MS. He sits on the International Clinical Consortium of the Guthy Jackson Charitable Foundation for NMOSD Research (CA, USA). He is a member of the scientific advisory board of the Swiss MS Society and the Drug Discovery Network Zurich (DDNZ).

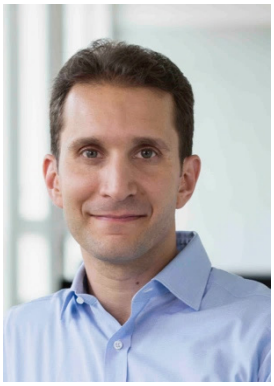
Lars Klareskog
Department of Medicine
Karolinska Insitutet, Stockholm, Sweden

Keynote lecture 3
"Pathogenesis of rheumatoid arthritis;
From triggering to targeting"

Biographical Sketch of Lars Klarsekog

Professor Lars Klareskog received his MD and PhD degrees from Uppsala University, Sweden, he specialized in rheumatology in Uppsala University Hospital and was professor of medical immunology in Uppsala 1990-1993. From 1993 he is professor of rheumatology at Karolinska Institutet, Stockholm, Sweden. He has been member of the Nobel Assembly/Nobel Committee at Karolinska Institutet 1996-2011 and chairman of the Assembly 2011. The main strategy in his research has been to establish rheumatology registers and biobanks, and combine these assets with molecular studies in order to better understand etiology and molecular pathogenesis of inflammatory rheumatic diseases, in particular arthritis. Progress from this research includes a better understanding of how genes and environment interact in contributing to the development of RA. This approach has also shown to be fruitful in designing clinical trials and in evaluating effects of therapy as well as prevention for these diseases. Awards given to Lars Klareskog and his groups for achievements in research and care include the Carol Nachman Prize (Germany) 2008 and, together with Peter Gregersen and Robert Winchester, the Crafoord Prize in polyarthritis (Royal Swedish Academy of Sciences) 2013.

Onur Boyman
Department of Immunology
University Hospital Zurich, Zurich, Switzerland



"IL-2-based approaches for induction of immune tolerance"

Biographical Sketch of Onur Boyman

After obtaining his M.D. degree from the University of Zurich, Switzerland, Onur Boyman trained as a postdoctoral fellow at the Scripps Research Institute in La Jolla, California. He then joined the Division of Immunology and Allergology of the University Hospital of Lausanne, Switzerland, as principle investigator and clinical fellow, before receiving in 2010 a professorship of the Swiss National Science Foundation. Since 2014, Onur Boyman has been professor and chair of clinical immunology at the University of Zurich and director of the Department of Immunology at University Hospital Zurich. Research in his laboratory focuses on the modulation of immune responses using cytokine-directed approaches, such as particular IL-2 formulations to stimulate regulatory versus effector T cells for selective immunotherapy, as well as pro-inflammatory cytokines and their inhibitors in chronic inflammatory and autoimmune diseases.

Roland Martin
Department of Neurology
University of Zurich, Zurich, Switzerland

"Role of the DR15 haplotype in MS"

Biographical Sketch of Roland Martin

Roland Martin is full professor for neurology and neuroimmunology at the University Zürich and heads the Neuroimmunology and Multiple Sclerosis Research Section and MS outpatient clinic at the University Hospital Zurich. R. Martin trained in medicine, and specialized in neurology at the University Würzburg. He pursued post-doctoral fellowships in immunology, virology and neuroimmunology in Würzburg and at the Neuroimmunology Branch, National Institutes of Health (NIH), Bethesda, USA, where he worked as tenured senior investigator until 2005. Subsequently, he held full professorships in Barcelona (Vall D´Hebron University Hospital), Hamburg (Director of the Institute for Neuroimmunology and Clinical MS Research, University Hamburg) and now in Zurich. The main interests of his group are disease mechanisms of multiple sclerosis (MS), cellular immunology, disease mechanisms of JC polyoma virus-mediated progressive multifocal leukoencephalopathy (PML) and developing novel treatments for MS and PML besides providing care for MS patients in one of the largest MS centers in Switzerland. He and his group developed more than 10 projects from idea to early clinical proof-of-concept trials. One of these projects (Daclizumab, an anti-CD25 monoclonal antibody; Zinbryta®) was just approved for the treatment of MS by EMA, FDA and Swissmedic. He is a member of the Kuratorium of the Jung Foundation for Science, Hamburg, of the core faculty of the Wyss Translational Center Zurich, a cofounder of the Drug Discovery Network Zurich (DDNZ) and of the Therapy Development Accelerator (TDA) at the University Zurich.

Simon Fillatreau
Immunity in Health and Disease
Institut Necker Enfants Malades, Paris, France

"Cytokine-producing B cells and plasma cells: Novel regulators of autoimmune diseases"

Biographical Sketch of Simon Fillatreau

S. Fillatreau studied biology at Ecole Normale Supérieure de la rue d'Ulm, Paris, France. He then did his PhD in the laboratory of Prof. David Gray at The University of Edinburgh, UK. He was appointed in 2003 as the head of the Immune Regulation group at the Deutsches Rheuma-Forschungszentrum, a Leibniz Institute Berlin, Germany. Since 2015, he is Professor of Immunology at the Faculté de Médecine de l'Université Paris Descartes. In 2015, he received the prestigious European Research Council consolidator award, and the GlaxoSmithKline Stiftung Wissenschaftspreise. He is AXA professor in Translation Immunology since 2016. His work investigates the role of B and T cells in autoimmune and infectious diseases. He contributed with pioneer studies to the identification of the suppressive role of B cells, and to the discovery of regulatory plasma cells. He showed that B cells could fuel autoimmune pathology not only through the production of autoantibodies, or the presentation of antigen to T cells, but also via the provision of pro-inflammatory cytokines. His team recently provided the first direct demonstration that endogenous self-antigens actually select thymic-derived autoreactive CD4+Foxp3+ T regulatory cells in a highly specific manner.

Mireia Sospedra
Department of Neurology
University Hospital Zurich, Zurich, Switzerland

"Search for candidate autoantigens in Multiple Sclerosis"

Biographical Sketch of Mireia Sospedra

Mireia Sospedra studied biology at the University of Barcelona and received her PhD on the induction of central tolerance to peripheral antigens at the Autonomous University of Barcelona under the supervision of Dr. Ricardo Pujol Borrell. After her PhD she moved to Paris in 1999 where she pursued a first postdoc at la Pitié-Salpêtrière hospital under the supervision of Dr. Alain Trautmann studying the interaction between T cells and dendritic cells in the absence of nominal antigen. In April 2001 she obtained a *competitive fellowship* from the *National Institute of Neuological Diseases and Stroke* (NINDS; at the *National Institute of Health* (NIH)) and moved to USA for a second postdoc. She started working in MS under the supervision of Dr. Roland Martin with a focus on the identification of new autoantigens. After four years at NIH, she returned to Barcelona 2005 with a career development grant/assistant professorship of the Catalan Institute for Research and Advanced Studies (ICREA) at the Neuroimmunology Unit (Vall d'Hebron Hospital) directed by Dr. Xavier Montalban. In 2007 she moved to Hamburg and started working at *Institute of Neuroimmunology and Multiple Sclerosis Research* (*Center of Molecular Neurobiology Hamburg, University Hospital Eppendorf) as independent investigator* studying T cell specificity in MS and also the role of neutrophils. Since September 2011 she heads the Laboratory of Neuroimmunology at the Neuroimmunology and Multiple Sclerosis Research Section at the Neurology Clinic, University Hospital Zurich, and University of Zurich.

Maarten Titulaer
Department of Neurology
Erasmus University Rotterdam, Rotterdam, Netherlands

"Autoimmune Encephalitis: antibodies you do not want to miss"

Biographical Sketch of Maarten Titulaer

Maarten Titulaer was trained as a neurologist in Leiden, the Netherlands combining residency with a PhD in Lambert-Eaton myasthenic syndrome and screening for lung cancer, for a small part as an ENS fellow at the University of Oxford. He continued as a clinical research fellow in Neuro-oncology and Immunology, funded by the Dutch Cancer Society, at the University of Pennsylvania with Prof. Dalmau, who discovered anti-NMDA receptor encephalitis and other antibodies causing encephalitis. He combined both clinical research in anti-NMDA receptor encephalitis and basic science in different forms of antibody-mediated encephalitis, first in Philadelphia, later at the University of Barcelona, also with Prof. Dalmau. Recently returned to the Netherlands, he has a faculty position at the Department of Neurology at the Erasmus Medical Center in Rotterdam. He runs an Autoimmune Neurology clinic, and combines clinical research with basic laboratory science in the field of Autoimmune Encephalitis.

Hans Lassmann
Institute of Neurology
University of Vienna, Vienna, Austria

Keynote lecture 4
"Relapsing versus Progressive Multiple Sclerosis: Pathology and Disease Mechanisms"

Biographical Sketch of Hans Lassmann

Hans Lassmann graduated from Medical School at the University of Vienna in 1975. He then joined the Institute of Neurology of the University of Vienna for training in clinical and experimental neuropathology. In addition he spent one year as a post doc at the Institute for Basic Research in Developmental Disabilities in New York. In 1990 he became director of the Research Unit for Experimental Neuropathology of the Austrian Academy of Science and in 1993 Professor for Experimental Neuropathology in the University of Vienna. From 1999 to 2007 he was the founding director of the Center for Brain Research of the Medical University of Vienna. He is currently Professor for Neuroimmunology at the Medical University of Vienna. He has received many research awards, including the Charcot Award (2005) of the International Federation of Multiple Sclerosis Societies for Life Long Achievement in Multiple Sclerosis Research, the Research Award (2000) of the SOBEK Foundation for outstanding research in multiple sclerosis and the K.J. Zülch Award (2010) for outstanding basic research in neurology. His current research activities concentrate on the pathogenesis of inflammatory diseases of the central nervous system with special focus on multiple sclerosis.

Reinhard Hohlfeld
Institute of Clinical Neuroimmunology
University of Munich, Munich, Germany

"What can twin studies tell us about the beginnings of MS?"

Biographical Sketch of Reinhard Hohlfeld

Reinhard Hohlfeld is Professor of Neurology and Co-Director of the Institute of Clinical Neuroimmunology, Ludwig Maximilians University of Munich, Germany.

http://www.klinikum.uni-muenchen.de/Institut-fuer-Klinische-Neuroimmunologie/en/index.html

His research interests include the autoimmune mechanisms and pathogenesis of neuroimmunological diseases, especially multiple sclerosis, myasthenia gravis, and inflammatory myopathies. He also has a long-standing interest in mechanisms (and risks) of immunomodulatory treatment.

Dr.Hohlfeld is a member of the advisory boards of the German MS Society and International Federation of MS Societies (MSIF); member of numerous editorial boards of scientific journals; elected member of the German Academy of Science (Leopoldina); and external scientific member of the Max Planck Society.

Ingrid Kockum
Department of Clinical Neurosciences
Karolinska Insitutet, Stockholm, Sweden

" Heterogeneity in MS – approached by studying gene and life-style exposure interactions."

Biographical Sketch of Ingrid Kockum

Professor Ingrid Kockum conducted her undergraduate studies at Newnham College, Cambridge, UK in natural sciences majoring in zoology with focus in molecular biology in 1989. She started her PhD studies in immunogenetics of type 1 diabetes at Lund University, Sweden and University of Washington, Seattle, USA, but defended her thesis at Karolinska Insitutet in 1995. She continued her research in the genetics of type 1 diabetes as a post doc at Wellcome Trust Center for Human Genetics, Oxford University, UK (1996 and 1997) and at Karolinska Insitutet, now focusing on the role of genes outside the MHC region.
Between 2001 and 2005 she lead the Multifactrorial disease genetics research group at the Department of Molecular Medicine and Surgery at Karolinska Insitutet where she studied genetics of type 1 diabetes, atopic dermatitis, bipolar disease and alcoholism. In 2006 she joined the Neuroimmunology Unit at Department of Clinical Neuroscience and changed focus of her research to genetic epidemiology of multiple sclerosis. In 2007 she became associate professor in genetics. Since 2016 she chairs the Nordic MS genetics group. Since 2014 she leads the Multiple Sclerosis genetic epidemiology research group at the department of clinical neuroscience. During the most recent years the groups research has focused on (i) identification of novel genetic susceptibility variants for multiple sclerosis a work that has been carried out mainly within the International Multiple Sclerosis Genetic Consortium (IMSGC) of which we are active members, (ii) identification of interactions between genetic and life-style risk factors for MS, (iii) study of expression control of genetic risk factors for MS and (iv) study of the role of viral infections in the susceptibility of Multiple sclerosis with focus on herpes and JC viruses.

Edgar Meinl
Institute of Clinical Neuroimmunology
University of Munich, Munich, Germany

"Humoral immunity in multiple sclerosis"

Biographical Sketch of Edgar Meinl

Edgar Meinl is professor since 2003 and group leader since 1999 at the Institute of Clinical Neuroimmunology at the Ludwig Maximilian University (LMU) Munich. He did his medical studies at the Justus-Liebig-University Gießen, followed by a postgraduate and thesis at the Clinical Research Unit for Multiple Sclerosis of the Max-Planck-Society in Würzburg under the supervision of Prof. Dr. H. Wekerle. Afterwards, he received a Post doctoral fellowship of the Max-Planck-Institute of Psychiatry in Martinsried, Dept. Neuroimmunology. From 1994 to 1999 he was group leader at the Institute of Clinical und Molecular Virology of the University Erlangen-Nürnberg (Director: Prof. Dr. B. Fleckenstein).

His research interest is in immunopathogenesis of Multiple Sclerosis.
He is editor for Clinical and Experimental Neuroimmunology, Journal of Pathology, PLOS One and Journal of Biological Chemistry (Reviewing Editor).

Andreas Lutterotti
Department of Neurology
University of Zurich, Zurich, Switzerland

"Antigen-coupled cells to induce immuntolerance in MS"

Biographical Sketch of Andreas Lutterotti

Andreas Lutterotti is assistant professor for "Experimental Therapy Research in Multiple Sclerosis and Other Neurological Diseases" at the University of Zurich since August 2014, as well as a senior physician at the Department of Neurology, Section Neuroimmunology and MS Research (nims), University Hospital Zurich. He has earned his medical doctor's degree at the Medical University in the Clinical Department of Neurology, Innsbruck was thereafter PostDoc and resident until 2012. During this time, he pursued an Alexander von Humboldt fellowship at the Institute of Neuroimmunology and Clinical Multiple Sclerosis Research in Hamburg. Subsequently, he returned to the Clinical Department of Neurology, Innsbruck, was certified in Neurology in 2012 and continued to work as a Senior Scientist. Andreas Lutterotti was appointed as assistant professor at the Department of Neurology, University Hospital Zurich, in August 2014. His core expertise is the development and implementation of experimentaltherapies in the field of multiple sclerosis and other autoimmune diseases. His research is supported by the UZH CRPP MS, the Wyss Translational Center Zurich and the Swiss MS Society.

YOUNG RESEARCHERS TALK

Proinflammatory B Cells Drive Brain-Homing and Pathogenic T Helper Cells in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis is a complex disease, caused by an interplay of genetic - most importantly HLA-DR15 - and environmental risk factors. How these etiologic factors generate and maintain an autoreactive $CD4^+$ T cell repertoire has remained elusive. Previously, we have shown that DR15-presented peptides are involved in increased T cell proliferation *in vitro* in multiple sclerosis patients. Here, we demonstrate that this "autoproliferation" is mediated by the interaction of proinflammatory B cells overexpressing HLA-DR molecules with CD4 and T cell receptors on $CD4^+$ T cells. Depletion of B cells *in vitro* and therapeutically *in vivo* by anti-CD20 almost completely abrogates T cell autoproliferation, while it is increased with rising circulating B cells in natalizumab-treated patients. A defined co-receptor signature, the proinflammatory cytokine interferon-gamma and several multiple sclerosis risk genes beyond DR15 are associated with increased autoproliferation. T cell receptor deep sequencing of brain-infiltrating and *in vitro* autoproliferating T cells shows that the latter are enriched for brain-homing T cells. Collectively, our data indicate that pathogenic T cells in multiple sclerosis are characterized by increased autoproliferation driven by proinflammatory B cells. These findings are instrumental to approach numerous questions on pathogenic T-B cell interactions in multiple sclerosis.

POSTERS

Abstracts

(In alphabetical order of presenting author)

CD8$^+$ T cells express inhibitory receptors but retain functionality during Epstein-Barr virus infection in vivo

Bithi Chatterjee[1], Liliana Danusia Vanaoica[1], Anne Müller[1], Tarik Azzi[2], Hana Zdimerova[1], Mark Robinson[3], David Nadal[2], Hanspeter Pircher[4], Christian Münz[1*]

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Keywords: CD8$^+$ T cell, EBV, T cell function, humanized mice

ABSTRACT
Epstein-Barr virus (EBV) infection and EBV-associated malignancies are underrepresented fields of research despite affecting millions of people. While EBV infection mainly occurs earlier and asymptomatically in children in the third world, people in the Western world often contract EBV later in life as a severe primary infection called infectious mononucleosis (IM) that poses significant health risks. EBV$^+$ individuals are at increased risk for malignancies such as post-transplant lymphoproliferative disease and for the autoimmune disease multiple sclerosis. Poor understanding of the in vivo pathogenesis of EBV and the lack of treatments available present a significant unmet medical need. EBV-specific CD8$^+$ T cells from IM and lupus patient samples express PD-1, a receptor that has been associated with poor immune control by T cells in a phenomenon known as exhaustion. We therefore wondered whether T cell exhaustion plays a role in EBV pathogenesis in vivo. We have examined human CD8$^+$ T cell exhaustion in EBV infection of human CD34$^+$ reconstituted NOD-scid IL-2Rγ-chain deficient mice. These animals reconstitute most major human immune compartments and expand CD8$^+$ T cells in response to EBV infection. Interestingly, CD8$^+$ T cells in infected animals upregulate and sustain multiple surface receptors that have been associated with T cell differentiation or dysfunction, including PD-1 and Tim-3. Despite this, proinflammatory cytokine levels are elevated and dose dependent in response to EBV. Moreover, these cytokines are produced by PD-1$^+$ T cell populations, indicating that T cells retain functionality despite the presence of inhibitory receptors. We also observe that CD8$^+$ T cells retain active proliferative capacity in the presence of PD-1. Efforts to determine the role of these receptors and of the T cell subsets that carry them during EBV infection and tumorigenesis are underway.

Reactivity of autoreactive T cells against post-translational modifications of brain proteins, specifically citrullinated peptides in MS

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Background: Reactivity against citrullinated proteins identifies a major subgroup of rheumatoid arthritis (RA) patients and numerous studies also link environmental factors like smoking or EBV infection with autoreactivity. Previous work in this laboratory has shown that reactivity against citrullinated MBP is elevated in MS patients. Moreover, smoking, which has been shown to contribute to citrullination of proteins in the lung, is an environmental risk factor in MS and RA. Finally, central tolerance mechanisms are expected to be less stringent against post-translationally modified self-proteins, since these should not be present or only to a limited extent in the thymus.
Objectives: It is suggested that citrullination/deimination of MBP induce the generation of new epitopes triggering as a consequence autoreactivity in MS. We aimed to identify new citrullinated peptides in MS versus normal brain tissue and to examine if brain-/CSF-infiltrating and peripheral blood T cells populations recognize citrullinated MBP or citrullinated peptides of other self-proteins.
Methods: Fresh frozen brain tissue from MS and controls cases were used in the proteomics study. Citrullinated peptides were identified by a combination of pressure cycling treatment and SWATH mass spectrometry providing information of the presence of new relevant citrullinated proteins/peptides in MS brains. The newly identified peptides will be used to address the recognition of brain- and CSF-infiltrating CD4+ T cells from MS patients measuring proliferation (3H-thymidine incorporation), cytokine production and other functions.
Results: The ongoing proteomics study already identified 8 new sites of citrullination in the MBP molecule that are expressed at high levels in the white matter of MS cases compared to healthy controls. Also, citrullination of glial fibrillary acidic protein (GFAP), a structural protein of astrocytes, is found more abundantly in the white matter of MS brains. Current experiments are ongoing to assess the CSF and peripheral blood T cell reactivity against newly defined citrullinated and the corresponding none modified brain epitopes in MS patients.
Conclusions: Citrullination appears to either promote a proinflammatory phenotype or afflict demyelination-remyelination processes, but could potentially also play other roles. Further investigation is needed to support that citrullination is linked with autoimmunity in MS and that T cells specific for citrullinated epitopes escape central tolerance.

EEG-based computational modeling of NMDA receptor function in multiple sclerosis

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Keywords: Dynamic Causal Modeling, NMDA receptor, Electroencephalography

There is a long-standing evidence that aberrant NMDA receptor (NMDAR) function plays a key role in MS and impacts on disease relevant processes both in a harmful and a favorable way (Rossi et al.,2013). In this regard, four relevant aspects have been identified that are related to NMDAR (dys)function: excitotoxicity, cerebral inflammation, remyelination, and compensatory plasticity. Unfortunately, we cannot presently measure NMDAR involvement in these processes non-invasively in the human brain.
One strategy for inferring these pathophysiological mechanisms in individual patients is to use a computational approach based on generative models. These are models which describe how observed data (e.g., neuroimaging or electrophysiological data) are generated by hidden mechanisms (e.g., synaptic interactions between neuronal populations). In this regard, biophysically interpretable dynamic system models such as Dynamic Causal Models (DCMs) have been developed and refined over the last decade, in particular for electroencephalography (EEG) data (Kiebel et al.,2009). Recently, biophysical models have been established that not only describe the interplay of excitatory and inhibitory neurons but also synaptic currents at various specific ion channels, including NMDARs (Gilbert et al.,2016).
Here, we present (highly preliminary) results from an ongoing EEG study in patients with early stage MS. Specifically, non-medicated patients with a clinically isolated syndrome or relapsing-remitting MS will be tested using EEG paradigms with known NMDAR-dependence (e.g. mismatch negativity). Using suitably defined DCMs, we will test the hypothesis that MS patients are, on average, characterized by alterations of NMDAR-mediated synaptic transmission and that model-based indices of NMDAR function are related to clinical changes over a 6-month follow-up period.

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Development of a large scale comprehensive human brain tissue expression database for Multiple Sclerosis

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Keywords: Multiple Sclerosis, human brain tissue, gene expression, database

Abstract

Multiple Sclerosis (MS) is the most common inflammatory disease of the brain with a chronic disease course and leads to long-term disability. Since no other species than the human sickens on MS, it is necessary that research can be performed with human brain tissue. Acquiring this tissue is challenging and such studies are often performed with a small number of cases. This has rendered any comparison between the different published studies very difficult. Our approach to this problem was to set up a comprehensive database containing 255 tissue blocks from 53 MS and 39 control cases. The database consists primarily of a whole genome gene expression analysis and a detailed histological quantification, but also contains patient data (e.g. age, gender), clinical data (e.g. length and type of MS disease) and data from the pathology (e.g. post mortem time, cause of death). The database is called MuSGED: Multiple Sclerosis Gene Expression Database.

First, all tissue blocks from control and MS cases were stained for particular cell markers and myelin allowing to identify regions of interest (ROI) of normal appearing white and cortical grey matter and grey matter lesions. In total we identified 647 ROIs of which we performed differential gene expression analysis and a quantitative immunohistochemical analysis. Currently, we implement the different data sets into an R (The R Project for Statistical Computing) database allowing us in near future to integrate and directly compare patient, differential gene expression and quantified histological data.

The database will lead to new insights on alterations between MS and control brains.

Also, any future samples can be interpreted against the strong baseline of our database, giving better quality to smaller studies performed.

Toll-like receptors are not involved in the onset of Experimental Autoimmune Encephalomyelitis

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Keywords: EAE, TLR, Pattern recognition receptors

Multiple Sclerosis (MS) affects approximately 2.5 million people worldwide but to date there is still no clear understanding on the factors initiating this disease. Studies in its animal model, Experimental Autoimmune Encephalomyelitis (EAE), suggest that an immune challenge is crucial for disease onset, as EAE can be triggered in mice after immunization with myelin oligodendrocyte glycoprotein (MOG) peptide in the presence of pertussis toxin and adjuvants. As most adjuvants contain bacterial components, danger-associated molecules, such as pathogen-associated molecular patterns (PAMPs) and, consequently, their pattern recognition receptors (PRR) must play a central role in EAE onset and progression. Some of these receptors, belonging to the Toll-like receptor (TLR) family, can recognise M. tuberculosis and drive an immune response through myeloid differentiation primary response 88 (MyD88). MyD88 has been shown to be required for EAE induction and therefore we theorised that the TLR pathway would be important to the onset of EAE. Moreover, we also predict that knocking-out several TLR would halt EAE development, as signalling through MyD88 would be impaired. To assess this, we took advantage of mice that simultaneously lack TLR 2, TLR 3, TLR 4, TLR 7 and TLR 9 (TLR 23479 KO). Surprisingly, in TLR23479 KO mice EAE develops in a similar fashion as in wild-type mice: There is no altered type-I interferon responses, no differences in CNS pathology and comparable amounts of pro-inflamamtory cytokine production between genotypes. These results demonstrate that knocking-out most of the TLR pathway upstream of the MyD88 does not impair immune response. Thus, there is the possibility that a TLR-independent pathway is responsible for EAE onset and progression.

A novel cervical spinal cord window preparation allows for two-photon imaging of T-cell interactions with the cervical spinal cord microvasculature during EAE

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Keywords: Cervical spinal cord window, Two-photon intravital microscopy, Experimental autoimmune encephalomyelitis, Blood-brain barrier

Abstract:
T-cell migration across the blood-brain barrier (BBB) is a crucial step in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Two-photon intravital microscopy (2P-IVM) has been established as a powerful tool to study cell-cell interactions in inflammatory EAE lesions in living animals. In EAE, central nervous system (CNS) inflammation is strongly pronounced in the spinal cord, an organ in which 2P-IVM imaging is technically very challenging and has been limited to the lumbar spinal cord. In addition cervical spinal cord lesions are seen in MS. We have therefore established a novel spinal cord window preparation allowing to use 2P-IVM to image immune cell interactions with the cervical spinal cord microvascular endothelium during EAE over extended time. We observed differences in the angioarchitecture of the cervical spinal cord versus the lumbar spinal cord, which will entail different hemodynamic parameters in these different vascular beds and thus may influence T-cell trafficking to different parts of the spinal cord. We presently employ this novel window preparation to directly compare the multi-step extravasation of encephalitogenic Th1 versus Th17 across cervical spinal cord microvessels in vivo. This analysis includes investigation of the cellular pathway of T-cell diapedesis across the BBB by visualization of endothelial junctions in this vascular bed.

RETINAL STRUCTURE AND FUNCTION IN MULTIPLE SCLEROSIS

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Keywords: multiple sclerosis, electrophysiology, optical coherence tomography

ABSTRACT
It has long been known that multiple sclerosis (MS) may influence the structure and function of the inner retina, optic nerves and visual pathway in the form of MS-related optic neuritis (ON). However, in recent years evidence is evolving consistent with structural changes distal to the inner retina and/or unrelated to a clinical history of ON. So far the functional correlates of such proposed structural changes remain unknown. We have thus embarked upon a comprehensive investigation of retinal structure and function in MS and clinically isolated syndrome (CIS) patients. A battery of electrophysiological tests enables functional measurements from the first-, second- and third-order retinal neurons in addition to the visual-evoked cortical response, whilst high-resolution optical coherence tomography (OCT) facilitates precise quantification of the corresponding retinal layers. Using this approach, we have documented functional changes of the outer retina in MS and CIS patients independent of ON, with inner retinal function becoming definitively abnormal only after ON. Structural changes were observed only after ON, and then only conclusively at the level of the inner retina. The findings suggest that primary dysfunction of the outer retina may be observed in MS and CIS without corresponding structural changes, whereas inner retinal dysfunction is recorded only in the presence of ON-related atrophy of the retinal ganglion cells (RGC) and their axons. In our early/benign cohort the outer retinal changes are relatively subtle in nature; future work aims to ascertain whether increased MS disease activity brings correspondingly increased outer retinal dysfunction.

Identification of the immunodominat T Cell Epitopes of AQP4 and MOG in demyelinating diseases

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Keywords: Aquaporin-4, Myelin oligodendrocyte glycoprotein, Neuromyelitis optica spectrum disorders, T cell epitope mapping

Background: T-cells, especially CD4+ T-cells, are key players in the pathogenesis of autoimmune diseases, which mediate cellular and humoral immune responses. Autoantibodies targeting the aquaporin-4 (AQP4)-water-channel-protein and the myelin-oligodendrocyte-glycoprotein (MOG) are associated with a broad spectrum of human CNS demyelinating diseases including neuromyelitis optica spectrum disorders (NMOSD) and acute disseminated encephalomyelitis (ADEM). Whereas the role of AQP4-specific T-cells has already been analysed in some studies, little is known about MOG-specific T-cells in these diseases. We therefore aimed to identify the immunodominant T-cell epitopes of AQP4 and MOG in patients with NMOSD. Methods: We performed a T-cell epitope mapping of human AQP4 and MOG peptides using the CFSE-proliferation assay. Peripheral blood mononuclear cells (PBMCs) of eight AQP4-antibody and four MOG-antibody positive NMOSD patients, one MOG-antibody positive ADEM patient, two patients with multiple sclerosis and ten healthy controls were stimulated with a library of eight AQP4 and nine MOG peptides. After eleven days, the proliferation of PBMCs in response to single peptides via the dilution of the CFSE-staining was analysed by flow cytometry. Furthermore, the cytokine secretion, particularly granulocyte macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-ɣ, interleukin (IL)-4, IL-6 and IL-17A was examined using ELISA. For investigating the differentiation of T-cells into distinct CD4+ T helper cell subsets, particularly Th1 and Th17 cells producing proinflammatory IFN-ɣ and IL-17A, respectively, a fluorescence-cytometry-based intracellular staining was performed.

Results: We detected higher peptide specific T-cell proliferation in response to AQP4 peptides in all NMOSD patients when compared to healthy controls. A T-cell response to MOG peptides, preferably to peptides corresponding to the extracellular immunodominant Ig-domain, was found in NMOSD patients as well as in healthy controls. The production of cytokines (GM-CSF and IFN-ɣ) correlated with T-cell proliferation.

Conclusion: To conclude, our study indicates a specific T-cell response to AQP4, but not to MOG, in patients with NMOSD. We expect that our results are important for the development of new individualised immune tolerance therapies.

Characterization of Myelin Peptide-Coupled Red Blood Cells

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Antigen-specific tolerance can efficiently be induced *in vivo* by intravenous injection of cells coupled with the target antigen using Ethylcarbodiimide (EDC). Our aim is to develop a therapeutic regimen employing autologous red blood cells (RBCs) coupled with seven myelin peptides to induce antigen-specific tolerance in multiple sclerosis patients. Preclinical studies with peptide-coupled splenocytes have suggested „cross-tolerance" as the main mechanism of induction of tolerance by this regimen. Following the chemical coupling process with EDC, peptide-coupled splenocytes undergo apoptosis and are processed by phagocytes in the spleen, where the coupled peptides are represented in a tolerogenic way[1].
The aim of the current study was to analyze the direct effects of the chemical coupling process on RBCs and to assess the biodistribution of peptide-coupled RBCs *in vivo*. The morphological and metabolic changes characterizing programmed cell death in RBCs, i.e. eryptosis, were analyzed *in vitro*. Coupling of RBCs with EDC leads to cytosolic calcium increase and phosphatidylserine exposure, both hallmarks of eryptosis[2]. Further, EDC treatment led to a reduced deformability of peptide-coupled RBC as observed by ektacytometry.
To elucidate the organs involved in the uptake of peptide-coupled RBCs, we injected RBCs coupled with fluorescently labelled peptides intravenously in BALB/c mice and analysed the biodistribution *in vivo* and *ex vivo* by bioluminiscence imaging. The analysis revealed the liver as one of the major organs involved in the uptake of peptide-coupled RBCs. Histologic analysis corroborate the results, demonstrating uptake of peptide-coupled RBCs in liver macrophages/Kupffer cells.
In summary, peptide-coupled RBCs exert hallmarks of eryptosis and are efficiently taken up by macrophages/Kupffer cells in the liver after intravenous injection.

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Non-canonical autophagy drives CD4$^+$ T cell reactivation during autoimmune CNS inflammation

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Keywords: autophagy, EAE, antigen presentation, oligodendrocyte injury

Abstract

Reactivation and expansion of autoreactive CD4$^+$ T cells within the central nervous system (CNS) are considered to play a key role in the pathogenesis of multiple sclerosis and its animal model experimental autoimmune encephalomyelitis (EAE). Autophagy-related proteins (ATGs) deliver antigens into MHC class II-containing compartments (MIICs) for recognition by CD4$^+$ T cells. The autophagy protein ATG5 is essential in recruiting intracellular substrates for lysosomal degradation during canonical macroautophagy. In addition, ATG5 is required for LC3-associated phagocytosis, a non-canonical autophagy pathway which delivers extracellular, endocytosed material to lysosomes and MIICs and can be induced upon recognition of phosphatidylserine (Ptd-L-Ser)$^+$ dying cells. Here, we report that mice deficient in the autophagy protein ATG5 in CD11c$^+$ cells (DC-Atg5$^{-/-}$) are resistant to EAE development following adoptive transfer (AT-EAE) of myelin-specific CD4$^+$ T cells. DC-Atg5$^{-/-}$ mice showed substantially lower frequencies of activated CNS-infiltrating CD4$^+$ T cells while the frequency of CNS-infiltrating CD8$^+$ T cells were similar. Although limited in expansion, effector cytokine production by CNS-infiltrating CD4$^+$ T cells was unaltered in DC-Atg5$^{-/-}$ mice as compared to control littermates (DC-Atg$^{+/+}$). Loading of DCs with surface Ptd-L-Ser-expressing oligodendroglial cells (ODGs) resulted in higher myelin-specific CD4$^+$ T cell activation as compared to low surface Ptd-L-Ser-expressing ODGs. Increased T cell activation upon loading with Ptd-L-Ser^{hi} ODGs was abrogated in ATG5-deficient DCs. Our data demonstrate a requirement for ATG5 in CD11c$^+$ APCs in driving the re-activation of myelin-specific CD4$^+$ T cells during the effector phase of EAE and suggest that LC3-associated phagocytosis of dying ODGs augments T cell-mediated CNS injury during autoimmune neuroinflammation.

FATE-MAPPING OF GM-CSF IN INFLAMMATION

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keywords: GM-CSF, transgenic mice, Neuroimmunology, experimental autoimmune encephalomyelitis (EAE)

Granulocyte macrophage colony-stimulating factor (GM-CSF) has emerged as a critical T cell-derived cytokine in tissue-targeted autoimmune diseases. Whereas in the steady state GM-CSF is primarily produced by stromal cells, under inflammatory conditions it becomes a main pathogenic feature of tissue invading lymphocytes. There are many open questions regarding the regulation of GM-CSF expression in steady state and in inflammation and the fate of GM-CSF expressing T cells and their progeny remain unclear. To answer these questions, we have generated a Fate-Map and Reporter Of GM-CSF (FROG) mouse line. We genetically engineered the *csf2* locus by using Crispr/Cas9-mediated homologous DNA recombination, resulting in EGFP and Cre-recombinase being co-expressed within the natural *csf2* locus. Tomato-FROG mice (FROG mice crossed with tdTomato reporter mice) show the specific expression of EGFP by GM-CSF expressing cells and tdTomato by both GM-CSF expressing cells and cells which have formerly expressed GM-CSF but seized to do so (ex-GM-CSF$^+$). In experimental autoimmune encephalomyelitis (EAE) T cells are a prominent source of GM-CSF. However, fate-mapping analysis using FROG mice reveals that natural killer cells and γδ T cells might be another source of GM-CSF in pro-inflammatory conditions. Furthermore loss of the IL-23 receptor, specifically on GM-CSF expressing cells, shuts down GM-CSF expression as well as inflammation solidifying the notion that IL-23 is critical for the genesis of GM-CSF expressing pathogenic T_H cells.

Isolation and characterization of autoreactive CD4$^+$ T cells in narcolepsy patients

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Keywords: narcolepsy, CD4$^+$ T cells, autoimmunity

Narcolepsy with cataplexy is a sleep-wake disorder caused by the selective loss of neuronal cells of the posterior hypothalamus that produce the neuropeptide hypocretin (HCRT). As a result, HCRT-1 levels in cerebrospinal fluid (CSF) are very low in >95% of narcolepsy-cataplexy patients. Accumulating lines of evidence, including a strong association with the HLA-DQB1*06:02 haplotype, support the notion that narcolepsy is an immune-mediated disorder that manifests in genetically predisposed individuals upon exposure to environmental factors. However, CD4$^+$ T cells against HCRT or other neuronal antigens have not been described so far.
In the present study, we aim to identify and isolate autoreactive T cells from narcolepsy with cataplexy patients by combining antigenic stimulation, T cell receptor (TCR) deep sequencing and T cell cloning. T cells from the blood of narcolepsy patients or healthy donors were initially expanded polyclonally with mitogen and IL-2 in microcultures to generate T cell libraries that were subsequently screened for their reactivity against a set of neuronal antigens. When available, T cells from CSF were also polyclonally expanded. This approach led to the isolation and characterization of CD4$^+$ T cell clones reactive against HCRT and other neuronal antigens expressed by HCRT-producing neurons in narcolepsy patients but not in healthy controls. Moreover, using overlapping peptides covering the entire protein length, the immunodominant epitopes of the autoantigens were identified. To study the TCR repertoire, expansion and localization in vivo, next-generation TCR sequencing was performed on total T cells from blood and CSF as well as on autoreactive T cells. Importantly, autoreactive T cell clonotypes could be tracked in the blood and CSF of narcolepsy patients. Collectively, these data provide the first evidence of autoreactive CD4$^+$ T cell clones that can recognize HCRT and other neuronal antigens in the blood and CSF of narcolepsy with cataplexy patients that might play a role in the disease.

Specific intrathecal inflammatory profile is associated with cortical damage: combined CSF and MRI stratification of MS patients at diagnosis.

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Grey matter (GM) damage is one of the main pathological substrates of physical and cognitive disability in multiple sclerosis (MS). Meningeal infiltrates and intrathecal inflammation are thought to initiate and exacerbate GM injury.
By combining molecular neuropathology, CSF analysis and MRI imaging, we aimed at identifying possible biomarkers of meningeal inflammation, GM damage and finally disease severity.
Gene and protein expression were analysed in meningeal and CSF samples from 20 post-mortem secondary progressive MS (SPMS) and 10 control cases. Furthermore, cytokine/chemokine CSF analysis and 3T-MRI were performed at diagnosis in two independent cohorts of MS patients (35 and 38 subjects), and in 13 healthy controls. CSF protein profiling was correlated with GM damage as visualized by MRI.
Increased expression of inflammatory cytokines (IFNγ,TNF,IL2 and IL22) and of a specific set of molecules related to sustained B-cell activity and lymphoid neogenesis (CXCL13, CXCL10,LTα,IL6,IL10), was detected in meninges and CSF of post-mortem MS cases associated with high levels of GM demyelination, increased meningeal inflammation and rapid disease progression. Similar profile, including inflammatory mediators (TNF,sTNFR1,IFNγ,IL8,MMP-2,Pentraxin3,sCD163) and molecules related to B-cell activity and lymphoid-neogenesis (CXCL13,CXCL12,IL6,IL10,BAFF,APRIL,LIGHT,TWEAK), was detected in CSF of MS patients with higher GM lesion loads at diagnosis in both the independent cohorts. In contrast, a pattern of regulatory molecules (IFN-α2,IFN-λ2,CCL25) was found associated with low levels of GM damage, both in the patient and post-mortem cohorts.
A specific CSF protein profile at the diagnosis is associated with different degree of intrathecal inflammation and GM demyelination. The similarity of such a CSF profile with that observed at death in rapidly progressive MS subtypes with extensive GM pathology, strongly reinforces the role of combined CSF and MRI analysis at disease onset and indicates its possible utility as a prognostic marker for MS course from early phase of the disease.

Using optical coherence tomography to assess retinal morphology in experimental autoimmune encephalomyelitis

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Keywords: EAE; optical coherence tomography; multiple sclerosis; optic neuritis

INTRODUCTION: Neuro-axonal injury plays a prominent role in early multiple sclerosis (MS) pathology and is a key contributor to non-reversible long term disability in patients. However, underlying mechanisms are not yet fully understood. Visual impairment is a common feature of MS in which episodes of MS-related acute optic neuritis (ON) are often followed by structural retinal damage that can be quantified *in vivo* using optical coherence tomography (OCT). Alterations in the optic nerve and the retina have also been described in experimental autoimmune encephalomyelitis (EAE). Therefore, investigating structural damage in the anterior visual pathway provides a potential model to assess neurodegenerative changes. The aim of this OCT/DTI-study was to investigate the basic mechanisms underlying MS-related retinal structural damage and the temporal sequence of visual pathway pathology in MOG-induced EAE mice.

METHODS: 7 EAE-MOG_{35-55} and 5 healthy female C57BL/6J mice were used in this study. A volume scan (25 B-scans; 512 A-scans; ART 50) was obtained using the Spectralis OCT-2 Plus device adapted with a 78 diopter lens. A circular grid was placed directly over the center of the optic nerve head and the thickness of the ganglion cell complex (GCC) was obtained. Diffusion tensor imaging (TE 26.5ms, TR 2500ms, 60 directions, 75μm^2) was obtained on a 7T Bruker MRI unit and the fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) was calculated in the optic nerve. Data was acquired at baseline, disease onset, peak, and remission. Generalized linear mixed model was used to account for intra-subject, inter-eye dependencies, group and timepoint. Correlation analyses assessed the relationship between GCC thickness, EAE disability scores and DTI parameters (corrected for multiple comparisons).

RESULTS: In EAE mice, a significant increase in GCC thickness was observed at onset ($p<0.001$) and a significant decrease at remission ($p < 0.001$) compared to healthy controls. The EAE group had significant GCC thinning at remission compared to all other timepoints ($p < 0.001$ for each). GCC thickness at remission was positively correlated with FA (rho=0.81, p=0.03) and AD (rho=0.91, p=0.001) and negatively correlated RD (rho=-0.81, p=0.02). GCC thickness was also negatively correlated with EAE scores at remission (rho_-0.80, $p<0.001$).

CONCLUSION: The GCC thickness changes in EAE mice may be reflective of what is generally observed in MS–related ON; an initial phase of swelling followed by decreased thickness (representative of neuro-axonal degeneration) over time. OCT is capable of investigating retinal architectural damage and the temporal sequence of neurodegeneration in the mice model of MS. The underlying cause for those alterations will be further investigated by histological analyses.

Multiple Sclerosis: Autoradiography

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Abstract:
The goal of our project is to identify potential targets for imaging disease progression in Multiple Sclerosis (MS) using positron emission tomography (PET). Several molecular receptors have been reported to be up/down regulated in MS pathology. Non-invasive detection and quantification of receptor density and expression using PET tracers is therefore of significant clinical interest for disease management and therapy. We have evaluated a number of potential targets, and based on our autoradiography results we have identified translocator protein 18KDa (TSPO) PET tracer [^{18}F]FEMPA, $GABA_A$ tracer [^{18}F]FMZ and CB2 radioligand [^{11}C]KD2 as potentially promising radiopharmaceuticals for the PET imaging of MS. Two of these radiotracers, [^{18}F]FEMPA and [^{18}F]FMZ, will be evaluated further in different MS animal models using in vitro autoradiography and in vivo PET-CT imaging. Also in vitro autoradiography studies are planned with postmortem MS brain sections. The information obtained from all these studies would provide the basis for selecting the most promising radioligand for PET imaging of MS patients.

Identifying CNS associated antigen-presenting cells: Who tells a MOG_{35-55}-specific T cell it has arrived?

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Keywords: Antigen presentation, CNS, $CD4^+$ T cells, EAE

Multiple sclerosis is a putative autoimmune disease of the central nervous system (CNS) that is initiated when self-reactive T cells enter the brain and become locally activated after encountering their cognate myelin antigens (Ag). When and where the disease-initiating APC/T cell encounters occur is unclear. Although several studies tried to address this question, most of the published data rely on methodology that does not allow drawing clear conclusions. For example, in 2005, we described that dendritic cells permit immune invasion of the CNS. However, this finding is based on the use of CD11c-MHCII transgenic mice (CD11c was shown to not being exclusively expressed on DCs) and bone marrow chimeras (irradiation was shown to interfere with blood-brain-barrier (BBB)-integrity and to induce CNS infiltration by monocytes).
In this study, we make use of the adoptive transfer (AT) model of experimental autoimmune encephalomyelitis (EAE), which can be induced by transferring activated MOG_{35-55}-specific $CD4^+$ T cells into unmanipulated recipient mice. The transferred T cells have been already primed *in vivo* but need to re-encounter their cognate antigen in the context of major-histocompatibility-complex (MHC) II-bearing APCs in order to recognize their target within the CNS. By utilizing MHCII-fl/fl mice crossed to different Cre-expressing mouse lines we can specifically delete MHCII expression across the entire landscape of APCs in the CNS *in vivo*.
We found that there are three major $MHCII^+$ cell populations within the steady state brain, namely macrophages, DCs and B cells. Interestingly, with the CX_3CR_1-$CreERT_2$ x MHCII-fl/fl strain we could exploit two distinct Tamoxifen treatment regimens resulting in differentially targeted CX_3CR_1-expressing cells. While a short and early Tamoxifen treatment (targeting microglia and macrophages) resulted in disease manifestation, continuous treatment of the recipients with Tamoxifen (targeting microglia, macrophages and DCs) resulted in complete resistance of mice to AT EAE. Interestingly, the only cell type, which is targeted with the continuous but not with the short-term treatment, are DCs. To verify that CNS-associated DCs and not macrophages present CNS Ag, we are currently inducing AT EAE in zDC-Cre x MHCII-fl/fl mice, which are supposed to specifically target conventional DCs.

Therapeutic Efficacy of low molecular weight polysialic acid in EAE

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Keywords: EAE/MS – polysialic acid – Siglec - autoimmunity

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) with inflammatory and neurodegenerative immunopathological characteristics. Currently available disease modifying therapies show modest efficacies in halting disease progression and are associated with severe side effects due to immunosuppression, reflecting the unmet medical need for therapeutic strategies that target both inflammatory and neurodegenerative mechanisms with negligible toxicity. Sialic acid binding immunoglobulin-like lectin (Siglec) receptors regulate innate and adaptive immune cell function through the recognition of their sialic acid containing glycan ligands. Polysialic acids (polySia) as enodgenous Siglec ligands comprises repeating sialic acid monomers with α2,8 linkages which has primarily been studied in the developing CNS and upon CNS injury where polySia promotes repair mechanisms. The efficacy and mechanisms of polySia to inhibit immunemediated CNS tissue injury in appropriate preclinical in vivo models of MS has not been investigated so far. CNS-invading monocyte-derived DCs (moDCs), the progeny of Ly6ChiCCR2+ monocytes, drive tissue inflammation during experimental autoimmune encephalomyelitis (EAE). We report that Siglec-E, the murine inhibitory receptor for polySia, is strongly expressed and upregulated on Ly6ChiCCR2+ inflammatory monocytes and on CNS-infiltrating moDCs during EAE. Therapeutic administration of the Siglec E-ligand α2.8-linked polySia stopped disease progression in EAE. Our data indicate that inhibitory Siglec signaling can be harnessed through therapeutic administration of polySia in order to limit CNS inflammation and tissue damage in a preclinical model of MS.

D**etailed Characterization of Global and Active TCRBV Repertoires in Brain-Demyelinating MS Lesions**

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Keywords: multiple sclerosis, T-cell receptor, deep sequencing, brain lesions

ABSTRACT
Specific activation of pathogenic T cells is considered essential in the initiation and maintenance of multiple sclerosis (MS). The site of activation, the different involvement of CD4+ and CD8+ T cells, their functional phenotype or specificity, are crucial questions to understand MS pathology. The analysis of clonal T cell expansions can reveal antigen-driven T cell activation and allow the identification of putative pathogenic T cells. Using high-throughput TCR beta chain sequencing (TCR-seq) of genomic (g)DNA, that reflects the quantity and diversity of the TCRBV repertoire, and complementary (c)DNA, that reflects the activation status of the T cells, we have analyzed, for the first time, the "global" (gDNA) and "active" (cDNA) TCRBV repertoires of three demyelinating brain lesions, with different location and inflammatory activity, and paired peripheral memory CD4+ and CD8+ T cell pools. Our results demonstrate a noteworthy overlap of the global but an insignificant of the active TCRBV repertoires between the three lesions, independently of their location or inflammatory activity, suggesting that a similar TCRBV repertoire infiltrates the three lesions but that distinct T cells are locally activated. Comparison with the peripheral T cell pools demonstrates that most of brain-infiltrating CD4+ but only active CD8+ TCCs are clonally expanded inside the CNS and most likely enriched in pathogenic T cells. Approaches to identify pathogenic T cells in brain lesions using TCR-seq can benefit by focusing in lesions with high frequency of active T cells and by using cDNA sequencing.

Detecting abnormalities of cerebral and extracterebral tissue oxygenation and blood perfusion using near-infrared spectroscopy (NIRS) – An innovative approach to quantify disease heterogeneity of multiple sclerosis in humans

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Keywords: Near-infrared spectroscopy, blood flow, tissue oxygenation, multiple sclerosis

Near-infrared spectroscopy (NIRS) enables the non-invasive measurement of cerebral and extracerebral tissue oxygenation and blood perfusion (Scholkmann et al., 2014). There are more and more reports about the impairment of cerebral metabolism and blood perfusion in multiple sclerosis (MS) patients (e.g., Doche et al., 2017; D'haeseleer, et al., 2015; Yang & Dunn, 2015). Interestingly, the findings of these metabolic and hemodynamic abnormalities seem to vary significantly between patients. Quantifying the abnormalities is therefore a suitable approach for individualized diagnosis of MS as well as for monitoring the MS disease progression. There seems to be a link in MS patients between abnormalities of tissue metabolism and blood perfusion, iron overload, oxidative stress and inflammation (Sing & Zamboni, 2009). Up to now, the assessment of abnormalities of cerebral metabolism and blood perfusion in MS patients has been conducted by magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) or positron emission tomography (PET). Since the application of MRI, MRS and PET is complicated and costly, NIRS could be a welcome alternative method. The application of NIRS to assess abnormalities of cerebral metabolism and blood perfusion in MS patients is novel, but initial studies have so far delivered promising results (e.g., the finding of reduced cerebral tissue oxygenation in MS, e.g. Yang & Dunn, 2015). Besides being used to measure the absolute tissue oxygenation (NIRS-based cerebral oximetry), NIRS is also able to characterize the reactivity of blood flow and metabolism to physiological changes, i.e. autoregulation – another aspect that seems to be impaired in MS patients (e.g., Viola et al., 2015).

In this contribution to the symposium the basic principle of NIRS and how to adapt if for future medical applications for MS patients will be summarized and discussed.

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Immunophenotyping of cerebrospinal fluid-infiltrating cells to dissect MS heterogeneity

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Key words: multiple sclerosis, pattern II demyelinating lesions, cerebrospinal fluid, B cells.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with marked heterogeneity in several aspects including pathological processes. Four histopathological patterns of MS have been described. Pattern II is characterized by antibody and complement deposition in addition to T cell infiltration. The existence of this pattern is supported by the expression of distinct chemokine receptors, a more favorable response to therapeutic plasma exchange, a unique serum antibody signature and the abundance of brain-infiltrating $CD4^+$ and $CD8^+$ T cells that release Th2 cytokines and are able to provide B cell help. The identification of patients with pattern II demyelinating lesions, who might benefit from treatments targeting B cells, might increase the efficacy of these treatments and significantly improve treatment decisions. In this context, our aim has been to examine whether we are able to identify a CSF-infiltrate suggestive of pattern II demyelination. In order to characterize CSF-infiltrating T and B cells, we have developed a 13-color immunofluorescence panel that allows monitoring up to 170 different cell subsets by a one tube staining procedure, which is critical since only small numbers of cells are available by a routine spinal tap. Using this panel, we have analyzed *ex vivo* CSF-infiltrating and paired peripheral blood cells from 80 subjects including MS and control patients. Our results demonstrated higher intrathecal frequencies of certain B cell subsets in MS patients compared with controls. Interestingly, two groups of MS patients with high and low frequency of defined B cell subpopulations suggestive of pattern II demyelination were found. Additionally, T cell phenotyping revealed an intrathecal increase of Th2-like cells in both $CD4^+$ and $CD8^+$ T cells under inflammatory conditions. Although these results were not specific for MS, this finding suggests the involvement of Th2-like cells in the pathogenesis of a subtype of MS. Although further analyses are needed, these results support our working hypothesis that phenotypic characterization of CSF-infiltrating cells might help in dissecting MS heterogeneity.

The role of brain pericytes in the regulation of leukocyte trafficking under homeostatic and pathological conditions

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Keywords: pericytes, immune trafficking, EAE

Under homeostasis lymphocyte trafficking into the central nervous system (CNS) is tightly controlled by the blood–brain barrier (BBB). In multiple sclerosis (MS) autoreactive leukocytes enter the CNS and cause demyelinating pathology. Although vast effort is made to understand the pathophysiology of autoimmunity in MS, knowledge about pathological changes of the CNS vasculature that permit the extravasation of autoimmune leukocytes is still limited. Though it was demonstrated that pericytes play an important role in the development of the BBB, further studies are needed to better define the role of pericytes in regulating immune cell trafficking in the CNS.
We use genetically modified, pericyte-deficient (*Pdgfb ret/ret*) mice. These animals show approximately 85% reduction of pericyte coverage in the CNS vasculature. We use an animal model of MS-experimental autoimmune encephalomyelitis (EAE) to investigate the role of pericytes in neuroinflammation. In this model, active immunization with myelin oligodendrocyte glycoprotein (MOG 35-55) peptide or an adoptive transfer with MOG 35-55 activated T-cell blasts is performed. The following techniques are used: immunohistochemistry, histochemistry, confocal microscopy, electron microscopy and flow cytometry.
The analysis of brains of adult *Pdgfb ret/ret* mice has shown increased extravasation of leukocytes into the CNS. These infiltrates were found mainly in the corpus callosum and in periventricular regions. Flow cytometry analysis demonstrated that, the number of $CD45^{high}CD11b^{+}$ myeloid cells was increased in pericyte-deficient CNS compared to control. Immunization of *Pdgfb ret/ret* mice with MOG peptide led to an early and strong atypical EAE phenotype.
Our data suggest that pericytes regulate several BBB characteristics and inhibit leukocyte extravasation into the CNS by contributing to the non-permissive properties of the endothelium during homeostasis, and restrict immune cell migration. Pericyte-deficiency changes the clinical phenotype in EAE. However, further characterization is needed to better define the role of pericytes in immune cell trafficking in the CNS.

Magnetic Resonance Imaging Based Microstructural Phenotyping of Animal Models of MS

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Keywords: Experimental Autoimmune Encephalomyelitis, relapsing disease type, MRI phenotyping

ABSTRACT

Our objectives are to evaluate and validate structural, functional and metabolic MRI readouts for detecting gray and white matter changes in EAE, the animal model of multiple sclerosis. In a longitudinal, preliminary study in a relapsing/remitting subtype in the rat we assessed changes associated with white and gray matter pathology, as well as explored functional and metabolic changes during disease development and progression. For this purpose, we acquired on a 7T Bruker BioSpec MR system imaging-based markers of inflammation (qT2, ADC, 1H-MRS for GSH, mI, glu, readouts for macrophage tracking after systemic injection of USPIOs 24h prior MRI (300 umol Fe/kg, 20 nm nanomag-D-spio, micromod Partikel-technologie GmbH, Germany), BBB leakage through enhancement 5 min after Gd injection (0.2 mL Dotarem®, Guerbet)) and neurodegeneration (MTR, 1H-MRS for NAA, T1w) and for characterizing changes in tissue microarchitecture (DTI, DKI). In addition, we obtained resting–state functional MRI time series for the detection of changes in functional networks, and 1H-MRS for the detection of changes in endogenous metabolism and neurotransmission. Data were obtained from 10 coronal slices (typically 125 x 125 x 500 um3) from 10 female DA rats (RT1av1 MHC haplotype, Janvier Labs, about 150g) induced with 25-75ug rMOG1-125 (AnaSpec Inc., Fremont CA, dose-finding pilot study) in CFA at different time points during disease development, before disease induction, at onset, first peak and remission, and second peak and remission, respectively. Preliminary analysis did not reveal differentiated lesions but rather diffuse effects which warrant further quantification and correlation with histology.

In addition to the relapsing rat EAE model based on the Dark Agouti strain we plan to assess the more progressive MS/EAE subtype based on the same strain (induced with MOG1-125 in IFA) and study, in these two models, modulation of disease course and severity, and on commensurate imaging-based biomarkers in response to neuroprotective treatment, e.g. with hydroxytyrosol acetate. We aim to establish readouts that are particularly sensitive and more specific to detect inflammatory and neurodegenerative processes associated with MS, as well as functional and metabolic MRI readouts that may serve as biomarkers to discern specific MS subtypes and their modulation in response to neuroprotective treatment.

Cervical spinal cord and brain magnetic resonance spectroscopy alterations in normal appearing white matter of multiple sclerosis (MS) patients at 3T

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Anatomical MRI findings has limited value in predicting patient clinical status or the future course of the disease. Magnetic resonance spectroscopy (MRS) provides the means of accessing biochemical information from the neural tissue thus holding potential for better characterization of the disease and clinical decision-making. In this study, we examined metabolic alterations in the normal appearing white matter (NAWM) of both the brain (periventricular NAWM) and the cervical spinal cord (SC) at C3/C4 in different subgroups of MS. We measured spectra in 15 healthy controls (HC), 28 relapsing-remitting MS (RRMS) and 5 secondary progressive MS (SPMS) patients. The RRMS group is subdivided into three groups based on whether the expanded disability status scale (EDSS) has decreased (RRMSd), increased (RRMSi) or been stable (RRMSs) within the last 12 months prior to the MRS examination.

Concentration differences between HC and the patient groups were observed in SC and B for tNAA/tCho (SC/B:p=[0.003,0.011]) and tCho/Cr (SC/B:p=[0.01,0.006]). Additionally, in brain only, differences were found for tNAA/Cr (p=0.027), mI/Cr (p=0.08), Glu/Cr (p=0.016) and tNAA/mI (p=0.05) ratios. Statistical significant differences (false discovery rate corrected) occur between HC and RRMS**i** in tNAA/tCho (SC/B: p=[0.003,0.017]) and tCho/Cr (SC/B: p=[0.019,0.007]. HC and RRMS**s** have a significantly different tNAA/tCho (SC: p=0.003]) and tCho/Cr (SC: p=0.019) ratio. RRMS**i** and SPMS differ in the brain Glu/Cr ratio (p=0.028) and RRMS**i** and RRMS**s** have different brain tCho/Cr ratio (p=0.007). tNAA/tCho of the SC significantly correlates with tNAA/tCho of the brain (p<0.001). Changed concentration values detected by MRS may be an indicator of altered metabolism in NAWM of MS patients reflecting inflammation and neurodegeneration or an aggressive course of RRMS. We observed changes in metabolite ratios such as tCho/Cr or tNAA/tCho in both brain and SC. Metabolites including tNAA, Glu, tCho and mI seem to have discriminative power with regard to distinguishing MS subgroups. tNAA/tCho might be a marker of global metabolic abnormalities in NAWM of MS patients. The sensitivity of brain and SC MRS to distinguish clinical subgroups of RRMS with a difference in previous EDSS scores evolvement holds the potential for the use of MRS in therapy monitoring.

Examining the role of MS-associated genetic risk factors in a humanized mouse model of Epstein-Barr virus infection

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More than one hundred genetic and environmental risk factors have been implicated in the autoimmune disease multiple sclerosis (MS). The presence of the HLA-DR2 MHC Class II haplotype confers the strongest genetic risk, however its contribution to disease remains poorly understood. Of the environmental risk factors, infection with Epstein-Barr virus (EBV) is strongly correlated with increased MS risk, especially in patients who have experienced infectious mononucleosis (IM), the severe acute form of EBV infection. IM synergizes with the HLA locus for a sevenfold increased risk to develop MS. The mechanisms behind this interplay are not known. Our study aims to use humanized mice as an *in vivo* EBV infection model to investigate T cell responses in animals reconstituted with donors positive for genetic MS risk factors.

Using our model of NOD-scid gamma chain-deficient (NSG) mice reconstituted with human immune system components (huNSG), animals reconstituted with HLA-DR2$^+$ donors showed hyperactivated CD4$^+$ T cells in the steady state. Furthermore, following EBV infection, these huNSG mice developed elevated blood viral titers, as well as higher frequencies of CD3$^+$ and CD8$^+$ T cells. Recently, genome-wide association studies have identified multiple single nucleotide polymorphisms (SNPs) that seem to increase the risk of MS. We find that a higher immune activation in HLA-DR2$^+$ donor-reconstituted animals is associated with certain SNPs in immune related genes, including endocytosis receptors, signaling molecules and transcription factors involved in antigen processing and differentiation of cytotoxic effector CD8$^+$ T cells. Thus, MS-associated genetic risk factors could predispose individuals to elevated, poorly protective T cell responses after EBV infection, possibly priming autoreactive T cell specificities in the process.

Molecular pathology of MS lesion tissue reveals a heterogeneous expression pattern of genes involved in oligodendrocyte development

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Little is known about the decisive molecular factors that regulate lesion remyelination in Multiple Sclerosis. To identify such factors, we performed a differential gene expression analysis of normal appearing white matter (NAWM), active lesion (AL), remyelinating lesion (RM), and inactive demyelinated lesion (IdL) tissue. Focusing on genes involved in oligodendrocyte development, we found, in comparison to NAWM, a decreased expression of NKX2-2 as well as SEMA3B in AL, RM and, together with SOX10, in IdL tissue. In contrast, the expression of CXCL12 (SDF1) was strongly increased in AL, RM and IdL whereas IGF1 and IGF2 were found to be higher expressed in IdL tissue. In addition, we found an increased expression of members of the STAT6 pathway such as STAT6, IL4 and IL4R in AL, RM and IdL tissue. This suggests that a protective, anti-inflammatory reaction already mounted in the NAWM, is further enhanced in lesion tissue. In conclusion, although oligodendrocyte developmental genes are present, no clear promoting or inhibiting pattern could be detected in neither of the different tissues. This might reflect the heterogeneity of lesion development in MS patients. Interference with a potent pro-remyelination drug might therefore influence and shift the expression pattern toward remyelination and lesion repair.

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